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Dr. Janet Woodcock, Director
Center for Drug Evaluation and Research
Food and Drug Administration
ATTN: Document Control Room
Metro Park North II – Room 150
7500 Standish Place
Rockville, MD 20855

RE: Citizen Petition Docket Number 98-0145

Dear Dr. Woodcock:

This letter is being provided in support of the Citizen Petition of Andrx Pharmaceuticals, Inc. regarding the need for further agency consideration of the requirements for controlled-release diltiazem products.

As one of the original preclinical and clinical investigators on diltiazem back in the late 70s and early 80s, it became clear that specific formulations can affect the delivery of the active molecule differently. We first noted a dose dependency in absorption in 1982 prior to the development of any of the sustained-release diltiazem products. Subsequently, three products were developed, all of which utilized a different delivery mechanism. Similarly, and for good reason, all of these products were listed as "BC" products by the FDA. This differentiation in therapeutic response associated with different formulations can have clinical impact, as noted in the February, 1994 Board of Pharmacy newsletter from the state of South Carolina. In this situation, renal transplant patients that were receiving a sustained-release diltiazem formulation to both prevent renal toxicity and raise cyclosporin levels, received a substitute formulation. Following the "generic substitution," four of these patients ended up back in the hospital and had to be retitrated. This situation provides a clear example of what can happen when one sustained-release diltiazem formulation is substituted for another.

In reviewing this bioavailability data, I would also encourage you to look at the number of patients that have their serum levels drop below 40-50 nanograms/ml during the 24 hours following dose. When I stipulated 40 nanogram/ml as the minimal effective concentration and evaluated bioavailability studies, I found a significant difference in the number of patients who were able to stay above that

98P-0145

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therapeutic level with the different "BC"-rated formulations that are currently available. In my experience, this therapeutic MEC provides a reasonable rule of thumb for patient response. Thus, for a formulation to be considered equivalent, it should maintain serum levels in this range over 24 hours as compared to the reference standard.

In summary, in the same manner in which the FDA considers Tiazac and Cardizem-CD to not be therapeutically equivalent, a "one-peak" diltiazem formulation should not be considered therapeutically equivalent to a "two-peak" formulation.

Sincerely,

Robert W. Piepho, Ph.D., FCP
Dean and Professor

RWP:jp